

Research to Practice



Neurobehavioral Problems Associated with Phenylketonuria

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INTRODUCTION

After medical school, most psychiatrists are not likely to think about treating phenylketonuria (PKU) in their practices. After all, PKU is a rare, genetic disorder of amino acid metabolism identified at birth by pediatricians and treated by geneticists.¹ But, PKU is also a disorder that, if left untreated, leads to severe behavioral difficulties and ultimately mental retardation. The identification of PKU during routine newborn screening and management with a diet low in phenylalanine became standard practice in the early 1960s, thereby averting the severe complications of PKU.

Nonetheless, cognitive and behavioral problems remain a significant cause of morbidity in the PKU population. Several studies have documented attentional deficits, school difficulties, and mood disorders among adolescents and adults with PKU.^{2–7} In addition, there remain the obvious psychosocial consequences for a young child or adolescent who has to deal with a chronic disease and special diet. Recently, with the advent of medication to help manage blood phenylalanine (phe) levels, there has been a greater effort to characterize the prevalent difficulties experienced by individuals with PKU. For this

column, I interviewed William Lang, MD, FACP, Senior Medical Director, BioMarin Pharmaceutical Inc., Marin County, California. Dr. Lang and BioMarin are exploring the effects of a medication, sapropterin dihydrochloride, on neuropsychiatric symptoms in patients with PKU with a clinical trial that is being conducted at more than 30 sites in the United States and Canada (Clinicaltrials.gov NCT01114737: Safety and Therapeutic Effects of Sapropterin Dihydrochloride on Neuropsychiatric Symptoms in Phenylketonuria (PKU) Patients).

CAN YOU TELL US ABOUT PHENYLKETONURIA (PKU)?

Dr. Lang: PKU was initially described by Felling¹ in 1934 when he associated mental retardation with elevated levels of phe in children. PKU is an autosomal recessive disorder that causes a deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH) that is required to metabolize phe to the amino acid tyrosine.⁸ There are more than 400 mutations associated with the PAH gene, which is located on chromosome 12. Phenotypically this wide assortment of mutations is associated with variable degrees of PAH dysfunction and consequently a wide range of elevations in phe levels across individual patients.

Elevated phe levels are postulated to cause morbidity through a number of mechanisms, including myelin sheath abnormalities and disruption of amino acid transport across the blood brain barrier, as well as neurotransmitter deficiencies, including reduced dopamine levels. If left untreated, a severely affected child will develop microcephaly, progressive cerebral damage, seizures, and major neuropsychiatric problems. Early, aggressive treatment to maintain phe levels within a prescribed range by dietary

management, however, has been very successful in averting virtually all of the complications of PKU in the large majority of well-managed patients. Nonetheless, dietary management is not without its problems. Maintaining a strict, low-protein diet and adhering to a dietary supplement regimen requires planning and discipline. It can also be expensive, and is quite unappealing to most patients in terms of taste and lack of variety. It can also be a significant

on restrictions on dietary intake of foods high in phe. For infants, specialized formulas are available that can be combined with carefully measured amounts of milk to yield the appropriate amount of phe-containing protein. As children grow and their diet expands, and especially as they begin to attend school and see what their peers are eating, dietary control becomes much more difficult. For some patients, the drug Kuvan® (BioMarin

poorer school performance. Keeping the phe level low is critical in the management of PKU.

WHAT ARE SOME OF THE NEUROBEHAVIORAL PROBLEMS FOUND IN PATIENTS WITH PKU?

Dr. Lang: Early identification of PKU and treatment with phe-restricted diets has really minimized the more severe cerebral damage and psychiatric problems associated with PKU, but there are still attentional, behavioral, and mood disorders that occur commonly in patients with PKU that frequently go unrecognized. As children and adolescents, patients with PKU may have learning difficulties, school problems, decreased motivation, less social competence, irritability, hyperactivity, mood disorders, and poor self esteem.²

Neuropsychiatric problems occur even in well-controlled patients, and there is a clear correlation between these problems and increased phe level. Thus whether a patient is maintaining a good diet or not is a critical issue. In 1967, the Maternal and Child Health division of the Public Health Service funded a 16-year PKU study. At the beginning of the study, 211 children were followed until they became teenagers. At age six, half of the group was assigned to continue the low-phe diet and the other half to stop the diet. Although the results yielded the recommendation that patients with PKU should stay on a low-phe diet for life, most of the patients stopped the diet anyway. In fact, only 9 of 70 patients (13%) who had been on the diets from the original long-term study had remained on the diet in a follow-up study.⁴ The most notable behavioral symptoms among those off the diet were hyperactivity, lethargy, and a variety of mental disorders including phobias, panic attacks, and depression.

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psychosocial burden for children and adolescents because it can isolate a child from his or her peers, as well. Suffice to say that maintaining prescribed phe levels can be challenging, and many patients do not attain sustained success.

HOW FREQUENTLY DOES PKU OCCUR?

Dr. Lang: According to the National Institute of Child Health and Human Development, PKU occurs in approximately 1 in 15,000 births in the United States. But, the incidence varies around the world based on ethnic populations. For instance, PKU occurs much more frequently in Ireland—approximately 1 in 4,500 births, but only 1 in 100,000 births in Finland. The highest rate of occurrence is in Turkey, where PKU occurs 1 in every 2,600 births.

HOW IS PKU TREATED TODAY?

Dr. Lang: There is no cure for PKU; however, blood phe levels can be maintained at low levels with special low-phe diets based primarily

Pharmaceutical Inc., Marin County, California) has been shown to lower phe levels and has been approved by the FDA for use in conjunction with a low-phe diet. Kuvan is also known as BH4 or sapropterin dihydrochloride. It is a naturally occurring, essential cofactor required for phenylalanine hydroxylase to degrade the amino acid phenylalanine. In some, but not all, patients with PKU, Kuvan can partially correct the metabolic error in phenylalanine hydroxylase and thereby lower phe levels.

Notwithstanding these medical treatments to lower phe levels, it is difficult to maintain tight control. Many patients with PKU have neurobehavioral problems that require psychotherapy and medications as well. In addition, it is not easy for anyone to stay on a diet forever, especially adolescents, and diet discontinuation is a big issue for patients with PKU. Diet discontinuation is associated with higher phe levels that, in turn, have been associated with more behavioral problems, mood disorders, and

FRANKLY, MANY ADOLESCENTS WHO DO NOT HAVE PKU DO HAVE ATTENTION DEFICIT PROBLEMS, HYPERACTIVITY, AND MOODINESS. ARE PKU PATIENTS REALLY DIFFERENT THAN NORMAL ADOLESCENTS?

Dr. Lang: Generally, when compared to groups of patients with other chronic illnesses, patients with PKU have more cognitive, mood, and functional difficulties. In fact, some comparative studies have revealed marked behavioral and psychosocial differences between adolescents with PKU and other unaffected adolescents. A German collaborative study of adolescent patients with PKU who were treated early revealed that they were twice as likely to develop severe psychiatric problems compared to a normative population of adolescents.⁴ Of course, patients with PKU with poor metabolic control had even greater problems. Recent studies⁴⁻⁷ suggest that even patients with PKU who continue treatment and maintain the prescriptive low-phe diet may still have poor self esteem and seek psychotherapy.

DO ADULTS WITH PKU HAVE NEUROBEHAVIORAL PROBLEMS?

Dr. Lang: Yes, the problems that begin in childhood do not disappear.⁴⁻⁶ The fact that many patients with PKU stop the low-phe diets is a large part of the problem.

The German collaborative study by Koch et al⁴ also studied adults with PKU. They identified depression and anxiety symptoms as the most frequent symptoms in this group. A more recent study by Simon et al⁶ noted that adult patients with PKU were more likely to live at home and remain unmarried than their unaffected counterparts. Behavioral problems occurred most frequently in patients who were off diet, but there were still behavioral problems found in patients who stayed on diet.

DOES PKU AFFECT INTELLIGENCE IN ADULTS?

Dr. Lang: Yes, it is clear that staying on the low-phe diet makes a big difference. In the long-term, follow-up study by Koch et al,⁴ the few patients with PKU who had maintained their diet had the best intelligence scores. Their IQ scores were within three points of their parents' scores, whereas the patients with PKU who had stopped the diet had IQ scores significantly lower

with a reduced-phe diet and low-phe protein supplements. Many patients also respond to sapropterin (Kuvan) with reduction in phe levels. Combined with diet, Kuvan can result in very good control of phe in a substantial proportion of patients with PKU. Beyond that, many patients with PKU may seek some form of counseling and others may take psychotropic medications as well. Many genetic clinics maintain close relationships with psychologists and

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than their parents. The difference was not just in test scores. Only 32 percent of the group who stopped the diet graduated from college, whereas 78 percent of those who continued the diet graduated from college or had a postgraduate degree.

IS THERE A BIOLOGICAL BASIS FOR THE NEUROBEHAVIORAL PROBLEMS ASSOCIATED WITH PKU?

Dr. Lang: As part of the catecholamine pathway, phe is a precursor for tyrosine that is usually converted to l-dopa via tyrosine hydroxylase and then to dopamine. It is no surprise that deficiencies on this pathway could lead to psychiatric problems.⁸

HOW DO YOU TREAT THE NEUROBEHAVIORAL PROBLEMS ASSOCIATED WITH PKU?

Dr. Lang: The first step to treating neurobehavioral problems associated with PKU is to manage the phe levels in the blood. This is generally done

psychiatrists who collaborate in a team approach to managing PKU. On the other hand, I believe that the full extent of the neuropsychiatric problems associated with PKU has not been not sufficiently studied. As part of the clinical trial we are currently conducting, we hope to better elucidate the extent and type of neuropsychiatric problems experienced by patients with PKU.

CAN YOU DESCRIBE THE STUDY?

Dr. Lang: We are studying adolescent and adult patients with PKU being treated with sapropterin (Kuvan). We will evaluate whether the medication combined with diet will reduce the neuropsychiatric symptoms associated with PKU in patients who experience a reduction in phe levels. Study participants will receive either Kuvan or placebo for 13 weeks, after which everyone will receive Kuvan for another 13 weeks. We will be evaluating attention deficit problems, hyperactivity, and a variety of mood and anxiety symptoms.

WHAT'S ON THE HORIZON FOR THE TREATMENT OF PKU?

Dr. Lang: In addition to treatment with a low-phe diet and Kuvan, there are experimental therapies being evaluated for PKU. One of these is PegPAL or pegylated phenylalanine ammonia lyase. This is an enzyme treatment that directly converts phe to tyrosine. Unlike Kuvan, it is not a cofactor for a dysfunctional enzyme (phenylalanine hydroxylase). Rather, PegPAL replaces the function of that enzyme altogether. If it is successful, it has the promise of being effective in all patients with PKU. For more information about PegPAL, see www.medicalnews.com/articles/153211.php.

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